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GAFRININ, A SESQUITERPENOID LACTONE FROM *GEIGERIA AFRICANA* GRIES—II

CONFORMATION

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Abstract—The NMR spectrum of gafrinin, a sesquiterpenoid lactone from *Geigeria africana* Gries, has been analysed in detail using decoupling techniques. The conformation of the cycloheptene ring has been determined from NMR coupling constants to be a slightly distorted boat.

THE structure of gafrinin has been derived from chemical and spectroscopic evidence.[1] The configuration of gafrinin was established by converting it to xanthumin.[2] We report here the detailed analysis of the NMR spectrum of gafrinin and derive the conformation of the cycloheptene ring from NMR coupling constants.

The 100 Mc/s NMR spectrum of gafrinin (Ib) is reproduced in Fig. 1. The two

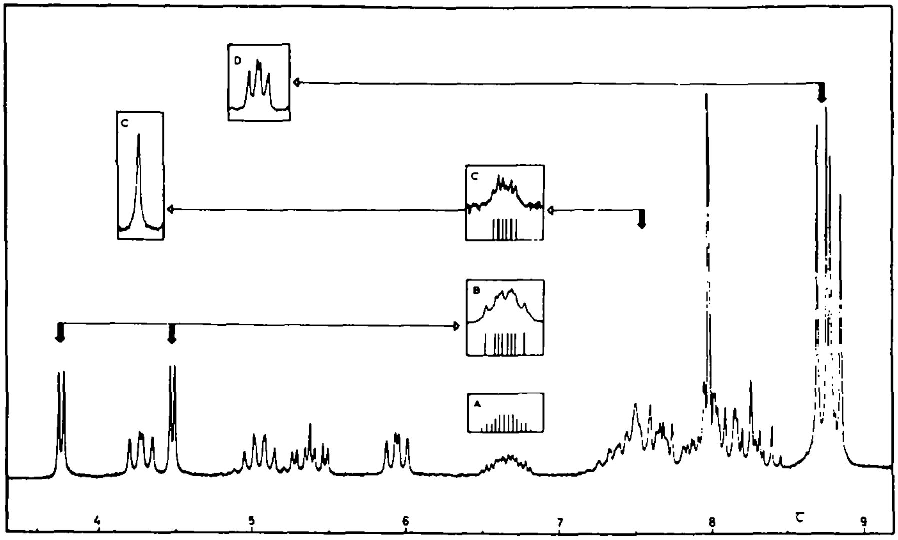

FIG. 1.

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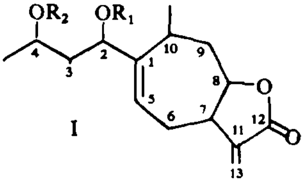
geminal protons on the exocyclic methylene group of the γ-lactone gave rise to the two characteristic doublets[3] at τ = 3·76 and τ = 4·48. The third olefinic proton (τ = 4·27) at C-5 shows two couplings (6·4 and 8·4 c/s) to a neighboured methylene group (C-6). The complex pattern at τ = 5·05 (basically a hextet) is assigned to the side-chain proton on the carbon bearing the acetoxy group as diacetylation shifts this signal to higher field (Ia, τ = 5·69). The proton on C-2 is similarly identified by the downfield shift of its NMR signal on acetylation (Ib, τ = 5·94; Ic, τ = 4·92). The remaining one-proton pattern in this range at τ = 5·37 therefore belongs to H-8. The 7-line pattern contains three splittings (11·6, 8·6, 3·0 c/s) due to interactions with H-7 and the protons of a methylene group (on C-9).



I

a $R_1 = R_2 = H$
b $R_1 = H$, $R_2 = Ac$
c $R_1 = R_2 = Ac$

The complex pattern at τ = 6·66 is attributed to the proton on C-7. The integral shows four further protons in the τ-range 7·2 to 7·8, one of which is the OH proton as it exchanges with D_2O. An acetyl peak at τ = 7·99 and the resonances of another four protons are found between τ = 7·8 to 8·5. The secondary Me resonance at τ = 8·82 is assigned to the C-10 Me, the other one (τ = 8·73) to the side-chain Me group.

Decoupling experiments confirmed and completed the assignments. Irradiating the signal at τ = 5·05 collapsed the doublet at τ = 8·73 thus identifying the side-chain Me. During the same experiment changes in the complex pattern between τ = 7·8 to 8·5 were observed. Two of the protons absorbing in this range are therefore of the methylene group in the side-chain. This was supported by decoupling the other side-chain methine proton (τ = 5·94) and observing changes in the same region. The other two protons absorbing in this range must be of the C-9 methylene group, as both the C-6 methylene and the hydrogen on C-10 are next to a double bond and their resonances should occur at lower field. Decoupling of H-8 at τ = 5·37 gave the expected perturbation between τ = 7·8 to 8·5, decoupling either H-7 or H-5 changed the pattern at τ = 7·2 to 7·8, confirming the assignments.

Irradiation of H-7 removed the coupling between H-7 and H-8 and collapsed the two doublets at τ = 3·76 and τ = 4·48. The H-8 pattern changed to a broad doublet with a spacing of ca. 11 c/s, proving that the splitting of 8·6 c/s is caused by the H-7, H-8 spin interaction. The doublet structure of the exocyclic methylene signals is due to allylic couplings with the H-7 proton, the geminal coupling being zero.

The resonance pattern of the H-7 proton is highly complex as it contains 5 couplings to H-8, the C-6 methylene protons and the exocyclic methylene group. It has been shown in the previous experiment that the coupling to H-8 is 8·6 c/s and this is confirmed by decoupling H-8 and observing the corresponding change in the overall line width of the H-7 signal. A triple resonance experiment (Fig. 1, insert B), which decouples both the exocyclic methylene protons, simplifies the H-7 pattern so far that the couplings to the C-6 methylene protons can be obtained. A good fit of the resulting pattern (insert B) is achieved with H-7, H-6 splittings of 6·0 and 11·0 c/s. Strong irradiation at $\tau = 7{\cdot}5$ decouples the H-6 protons, collapsing the olefinic proton H-5 to a singlet and simplifying the H-7 resonance to a 6-line pattern (insert C) which is well reproduced with splittings of 8·6, 3·3 and 2·7 c/s. Finally, the undecoupled H-7 pattern is seen to fit convincingly to the theoretical spectrum obtained with the five splittings of 11·0, 8·6, 6·0, 3·3 and 2·7 c/s (insert A).

The couplings of the side-chain methine next to the acetoxy substituent to the neighbouring methylene group are derived by decoupling the methyl group at $\tau = 8{\cdot}73$ (insert D).

The couplings derived in the previous section yield the conformation of the 7-membered ring. The cycloheptene system—in contrast to the flexible cycloheptane ring[4–6]—has two energetically favoured conformers analogous to chair and boat form of the cyclohexane ring[5,6] (Fig. 2), the former being considered more stable.[7]

FIG. 2.

Comparison with xanthumin[1,2] has established that the γ-lactone is *cis*-fused to the heptene ring. The coupling between the protons H-7 and H-8 (8·6 c/s) agrees well with an approximately eclipsed conformation of these protons (dihedral angle ca. 10°). Each of these protons interacts with the protons of a neighbouring methylene group (on C-6 and C-9, respectively) with a large ($\sim$11 c/s) and a small coupling. Each of them must therefore form dihedral angles of ca. 180° and 60° with its neighbouring methylene protons. An inspection of models shows that this is possible only if the lactone ring is α-*cis*-fused to the cycloheptene boat form as depicted in Fig. 3. Neither of the two chair-forms nor the β-fused boat form fit the NMR couplings (Table 1).

The other couplings within the ring system also agree with the suggested conformation. The C-6 methylene protons form angles of ca. 30° and 150° with the plane of the double bond (C-1, C-5, C-6) and the H-5, H-6 splittings found (6·4 and 8·4 c/s) are as expected if a Karplus-type relationship[8] between the dihedral angle and the magnitude of the vicinal coupling constants also holds for systems incorporating an sp^2-hybridized carbon.

Allylic couplings vary between 0 and 3 c/s and are dependent on the angle formed by the C—H bond and the C—C═C plane,[9] being largest for a rectangular arrangement. The corresponding angle in gafrinin is close to 90° and the allylic couplings found (2·7 and 3·3 c/s) are as expected. The smaller of these couplings corresponds to the cisoid configuration in contrast to previous findings.[9]

The C—10 Me group has been placed in an α-position (Fig. 3) as in xanthumin. Non-bonded steric interactions between the Me group and the quasi-axial proton on C—6* would tend to change the conformation in a manner which would also release the strain of the lactone ring, which is not quite planar.

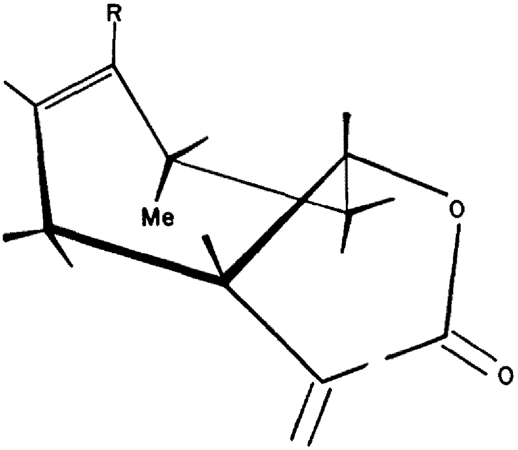
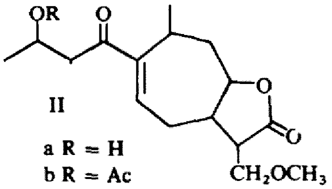


FIG. 3.

TABLE 1.

Conformer	Dihedral angles for ideally staggered conformers	
	△ H-6, H-7	△ H-8, H-9
α-Chair	60°, 180°	60°, 60°
β-Chair	60°, 60°	60°, 180°
α-Boat	60°, 180°	60°, 180°
β-Boat	60°, 60°	60°, 60°
Required from NMR couplings	60°, 180°	60°, 180°

The degree of distortion may be derived from the H-9 H-10 NMR coupling constants. The resonances of these protons were unfortunately obscured in the spectrum of gafrinin, but two closely related derivatives (IIa and IIb) could be analysed to give the required data. As the H-7, H-8 and H-8, H-9 splittings are very



II

a R = H
b R = Ac

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* The distance measured from models is close to 0 Å.

much the same as in gafrinin, no serious conformational differences between the parent compound and the derivatives IIa and IIb are expected. The splittings between the H-10 proton and the quasi-axial and quasi-equatorial protons on C-9 in compounds IIa and IIb were 7·5 and 0 c/s, respectively. Applying the Karplus equation[8] to the measured couplings, one has to conclude that the dihedral angles between the C—10—H bond and the C—9 methylene group are approximately 30° and 90°. This conformation shows a reasonably increased distance between the quasi-axial H-6 hydrogen and the C—10 methyl group. Thus the conformation of the cycloheptene ring in gafrinin is a slightly distorted boat.

No conclusions regarding the conformation of the side-chain can be drawn from the NMR data although the differences in the couplings between a particular methine and the methylene group indicate preferred rotational conformers.

EXPERIMENTAL

Spectra were obtained from saturated $CDCl_3$ solns on a Varian HA-100 spectrometer with TMS as internal reference at a probe temp of 32°. Chemical shifts, given as τ-values, are estimated to be accurate to ±0·01 ppm, coupling constants to ±0·1 c/s. Decoupling experiments were performed in the frequency sweep mode using a Hewlett-Packard 200 CD audio oscillator and a Hewlett-Packard 5521A electronic counter.

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